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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,869	05/14/2001	Howard Federoff	176/60088 (6-11406-600)	9948

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,869	FEDEROFF, HOWARD	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 may 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 6, 2004 has been entered.

Applicant's amendment filed July 6, 2004 (corrected claim set filed July 29, 2004) has been entered. Claims 67-76 are pending. The declaration by Howard Federoff, M.D., Ph.D., filed July 6, 2004 has been considered but is not found persuasive for reasons provided below.

Applicant had filed a Terminal Disclaimer on September 29, 2003 against the claims in US Patent 6,252,130 B1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of activating a gene to be expressed in a recombinatorial substrate and methods of activating a recombinatorial substrate comprising providing a transgenic non-human mammal carrying a DNA molecule comprising a recombinatorial substrate, does not reasonably provide enablement for methods of activating a gene to be expressed in a recombinatorial substrate and methods of activating a recombinatorial substrate comprising providing a transgenic mammal carrying a DNA molecule comprising a recombinatorial substrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection to "humans" is reinstated in view of the scope rejection above and given that the '130 patent is directed to nonhuman transgenic mammals. The only possible scope for

which applicant could gain would be to transgenic humans. This is being done for purposes of compact prosecution.

The claims are not enabled, as the specification does not teach methodology required for the production of transgenic humans. The art of transgenic animal production has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms that prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) in states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al.(1996) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al (1996) J. Clin. Invest. 98, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role

the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Applicant has not provided any guidance as to promoters or nucleic acid constructs that would lead to a transgenic human that when the recombinatorial substrate is expressed, the substrate will confer a detectable and/or functional phenotype on the human. The lack of enablement is particularly noteworthy as to the breadth of "detectable and/or functional phenotype" as presently claimed. This includes any phenotype from a highly complex disease phenotype such as that seen in Alzheimer's disease.

Further, the methods of activating a gene are only enabled for a transgenic mammal. The specification only discusses the use of a mammal where the recombinatorial substrate is integrated into the genome of the mammal's cells, making it transgenic. The specification teaches the production of these mammals by transgenic technology that is by the injection of a nucleic acid construct comprising the recombinatorial substrate into a fertilized egg. This technology will inherently produce mammals that have the nucleic acid integrated into some if not all of its cells. The specification provides no guidance or contemplation for the administration of the nucleic acid comprising a recombinatorial substrate in vivo to a mammal where the integration of the nucleic acid occurs in only localized areas of the mammal's organs and tissues. The specification only discloses and contemplates the localized induction of recombination. Additionally, the claims state

that the "recombinatorial substrate being present in somatic cells of the mammal." While this encompasses chimeric mammals that only have the recombinatorial substrate in some of its cells, it also encompasses a mammal that has the recombinatorial substrate in all of its cells. The only method of chimerism enabled by the specification is the random chimerism that results from the production of transgenic mammals. Most importantly, applicant has not contemplated the use of chimeric mammals produced by ES cell technology. The only mention of ES cell technology refers only to the introduction of the nucleic acid "the introducing step may be carried cut by microinjection or by introducing the DNA molecule into a blastocyst of an embryo or into embryonic stem cells" (specification, page 16, lines 5-7.) A mammal produced in this fashion is unpredictable because there is no means to control which tissues and organs contain the recombinatorial substrate. For example, if one wished to state gain of function or loss of function of a particular DNA sequence in the liver, there is no means to predictably direct the resulting chimeric mammal to contain the DNA sequence in liver. Likewise, even if cells containing the recombinatorial substrate present in a organ or tissue of interest, technology is not available to cause the recombinatorial substrate to be present in a useful number of desired cells. Thus, a chimeric animal that would be useful for the disclosed use to study the effects of a loss or gain of function is unpredictable, and not enabled by the specification. In particular, if chimeric is meant to include situations where the mammal's tissues and organs contain cells where the recombinatorial substrate occurs extrachromosomally, this is also neither contemplated by the specification nor does the disclosure enable the production of such mammals, where the mammals would have a use in the claimed invention. It is not seen how an extrachromosomal recombinatorial substrate would function for the disclosed study of gain or loss of function. One issue is would recombination occur if the substrate were located on an extrachromosomal piece of DNA? If, recombination would occur, then there would be other issues concerned with tissue distribution because when the cell divides, the extrachromosomal material does not divide with it such that the daughter cells would each contain the recombinatorial substrate. Thus, the only

enablement is when the mammal is a transgenic, where the DNA sequence comprising the recombinatorial substrate actually is integrated into the genome of the mammal.

Applicant argues that the term "transgenic" refers to the presence of a foreign gene in a cellular context, where it can be either integrated or as an episome. Applicant argues that cells that harbor a foreign piece of DNA can be considered to be transgenic. Applicant argues that in the common usage of the term "transgenic" refers to mammals that carry stably integrated copies of a gene of interest that is conveyed to their progeny. Applicant argues that this conventional techniques does not necessarily result in a mammal that has the foreign gene integrated into the genome of all of its cells. These mammals would be considered to be chimeric. Declarant Federhoff states that Gordon et al and Pinkert teach that transgenic means that the DNA sequence is carried by the animal as integrated into the genome or as a episome. These arguments are not persuasive.

Gordon et al, does not contain a clear definition of the term transgenic. In particular, Gordon et al does state that the mouse with the DNA sequence of interest as an extrachromosomal structure is transgenic. The closest Gordon arrives to a clear definition is in the discussion of mouse If4 being transgenic and then teaching that t his mouse has the If4 gene integrated into its genome. Gordon does not therefore support applicant's definition of transgenic. Pinkert also fails to support applicant's definition of "transgenic." Pinkert states "in gene transfer, animals new genes (integrating foreign DNA segments into their genome) are referred to as "transgenic," a term first coined by Gordon and Ruddell (1981)" (Pinkert, page 7, lines 4-6). Pinkert continues to say that the term "transgenic" has been expanded to include "either animals integrating foreign DNA segments into their genome following gene transfer or resulting from the molecular manipulation of endogenous DNA" (Pinkert, page 7, lines 9-12.) Thus, the art regarded transgenic mammals at the time of filing to have the foreign DNA sequences integrated into their genome.

Applicant is correct in the statement that a "transgenic mammal" might not have the foreign DNA sequences integrated into the genome of all each an every cell. In this regard, one could argue that there are no transgenic mammals, that all are probably chimeric. However, it appears from both Gordon et al, and Pinkert et al that true transgenic mammals have the ability to pass the foreign DNA to their progeny. This, however, is delving too much into technology than is necessary for the present invention. Transgenic mammals are regarded, at least as gleaned from a reading of Gordon et al and Pinkert, to contain a foreign DNA sequence integrated into a sufficient number of its cells to be useful for the purpose intended. In the present invention, the reason for the mammals or the use of the mammals is to study the gain of function or the loss of function of a DNA sequence of interest (specification, page 1, lines 15-20). The examiner agrees with applicant's assessment that the transgenic/chimeric animals would only need to have subset of cells carrying the recombinatorial substrate. However, where there might be disagreement is with the integration of the recombinatorial substrate into the genome. If the mammals are chimeric because they have the recombinatorial substrate as an extrachromosomal entity, then, these mammals are not enabled for reasons present above with regards to how to make them. Each method of the specification involves the production of transgenic mammals with the recombinatorial substrate integrated into the genome. Genetically manipulated ES cells have the foreign DNA sequences integrated into their genome.

Applicant argues that the invention claimed has potential for human therapeutic importance and was a driving force for the development of the claimed methods. Applicant points to several diseases involving inborn errors in metabolism as being candidates for treatment with the claimed methods. Applicant argues that the replacement of the missing and mutated enzymes involved in metabolic diseases can be accomplished in a subset of cells. Applicant argues that the correction can be achieved through the administration of gene-modified bone marrow-derived cells. Applicant argues that other somatic cells could also be used to correct these deficiencies. Applicant states that an individual with one of these disease would have a

somatic cell population engineered to carry a recombinatorial substrate that would contain an inactive form of the deficient enzyme. These arguments are not persuasive.

Neither applicant nor declarant has pointed to disclosure in the specification that supports the treatment of inborn errors of metabolism or any disease. Applicant is not permitted to identify a new use post-filing for their invention. The specification discloses the present method to be useful for "studying the cellular interactions that underlie the development and function of tissues and organs" (specification, page 1, lines 23-26; to develop in mammals an approach to study gene product function in varied organ systems such as that has been developed in Drosophila (specification, page 8, lines 11-22); and evaluating "a behavioral correlation of unilateral NGF mosiacism within the dorsal hippocampal formation" (specification, page 22, lines 31-34). None of these statements relate to disease treatment.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggested methods of methods of activating a gene to be expressed in a recombinatorial substrate and methods of activating a recombinatorial substrate comprising providing a mammal carrying a DNA molecule comprising a recombinatorial substrate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

September 19, 2004